If the many properties of the epidemiologic pattern of lung cancers created already some serious doubts concerning an unrestricted validity of the cigarette theory, this reaction received additional support when the medical evidence is subjected to a scrutinizing analysis. Through such a procedure a considerable number of important shortcomings in the methologic approaches employed become apparent which pertain to statistical methods employed, the techniques of data collection used, the types of data collected, their interpretations, and the conclusions arrived from a material which contains methodlogic vagaries, uncertainties, and predilections and from evidence which reveals serious inconsistencies and deviations from the usual behaviour of environmental carcinogens and from which at several instances arbitrary deductions have been made.

A. Methodological Uncertainties in Biostatistical Data

As an appropriate introduction to the discussion of this aspect to the cigarette theory of lung cancer a statement of MacDonald in regard to the precautions to be observed may be quoted; " Care must be exercized by the epidemiologist to evaluate all purported sharp increases in cancer at sites under the glare of extraordinary popular attention, so that the true state of affairs will not be submerged by a popular and understandable stampede to find a correlation between what may in fact be accidental, simultaneous occurrences and to take the next step and attribute to this correlation the property of causation".

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Adequacy of Statistical Method Used

Since various studies of the reliability of lung cancer diagnoses gleaned from death certificates have proved the unsatisfactory source of such information (Willis; Phillips; Hakarna and Saxen; Gilliam; Barkley and Bonser and Thomas) and since evidence based on autopsy findings are Phillips;

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

Table 45

The Relative Frequency Between Tobacco Smoking and Lung Cancer; Degree of Smoking Habit Among Lung Cancer Patients (Males).

Authors	Highly Excessive	Very Heavy	Heavy	Moderate	Mild and Non-Smokers	
Schrek et al.	18.3		50.0	12.2	14.6	Cigarettes, only, balance pipe and cigars
Wynder and Graham	20.3	30.9	35.2	12.4	1.3	
Doll and Hill	2.8	21.6	35.0	36.0	4.5	
Breslow	15.3	50.7	19.5	3.5	9.0	
Gsell	30.0	37.0	21.0	10.5	2.0	
Controls :						
Wynder and Graham	7.6	11.5	35.6	30.5	14.6	
Doll and Hill	0.9	11.3	31.8	42.0	14.0	
Breslow	3.5	34.8	18.8	11.1	30.5	

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Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

derived from a selected and therefore biased population, it has been generally agreed that a true estimate of the increase of lung cancers during the past 50 years as well as of their progression rate during this period in different countries is not feasible and that all statements made on these aspects of the lung cancer problem include a distinct share of educated guessing. It follows from this admission that all claims of a parallelism between the lung cancer increase and the rise in the consumption of cigarettes also contains a definite factor of scientific uncertainty especially in quantitative respects and particularly as evidence indicating a direct causal relation.

Practically all of the retrospective studies on the association between lung cancer liability and cigarette smoking have used information which was obtained from relatives and acquaintances concerning the degree and duration of the cigarette consumption by the individuals which died from lung cancer. Not only in every court of law such testimony would be inadmissible as totally unreliable, but it scarcely measures up to rudimentary scientific requirements. In fact, it is doubtful whether long time smokers or former smokers can recall correctly in many instances the duration and degree or type of smoking they engaged in over a period of several decades. It is surprising therefore that despite these serious and obvious factual handicaps most investigators of such associations have been able to demonstrate not only statistically significant correlations between cigarette smoking and lung cancer through the evaluation of data of this derivation but showed also the existence of a consistent gradient between the relative amounts of cigarettes smoked by these individuals and their relative liability to acquire lung cancers. The considerable variations reported by various investigators in regard to the degree of this gradient found for nonsmokers, pipe and cigar smokers and cigarette smokers of different grades of severity perhaps reflect to some extent the defects in the nature of the basic data used in such assessments. Table 45

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Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

The degree of reliability and significance of the calculations based on data of such quality cannot be improved by the use of exact and complex mathematical methods which are bound to yield results of dubious validity and of deceptive pseudoexactness.

It is for these and other reasons not surprising that several competent and experienced biostatisticians and epidemiologists have challenged the acceptability of the various claims made from an appraisal of such data. Berkson pointed out that such calculations had not taken proper consideration of the following aspects: increased longevity of the population altering the general cancer and disease panorama; limitation of the lung cancer mortality to only 10-15 % of the ciggrette smokers pointing to the action of other factors; disregard of the possible operation of constitutional factors influencing individual cancer proneness; lack of appropriate randomization of the population samples used in the statistical studies of cigarette smokers and of control groups. Berkson proposed that deaths from lung cancer represented a compensation phenomenon in response to a decrease of deaths from other diseases.

Berndt pointed in his criticism of the confirmatory studies to faulty methodology employed by excluding important variables from consideration and by using inadequate controls.

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Oppers and Hoelake noted the influence which competition of mortality rates might exert on the meaning of the results reported in favor of the cigarette theory. They pointed to the fact that, according to their studies of Dutch military personnel, nonsmokers of the age 40-50 years are 5.3 kg. heavier than heavy smokers and therefore should have on the basis of existing statistics a higher death rate than smokers. Such reversed relationships might in their opinion introduce a subtle bias into the observations of adherents of the cigarette theory. They argued that the high death rate among smokers might be a statistical fiction and that the demonstration of correlations

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

between lung cancer and cigarette smoking did not establish a causal association.

While the introduction of the cohort and prospective method of statistical investigation represents doubtlessly a distinct improvement (Case; Clemmesen; Doll), even these procedures can not eliminate the possible bias introduced into such calculation through the failure of a considerable proportion of the members of a population group to answer questionaires. Almost 50 per cent of about 7800 Canadian veterans failed in this respect. It is likely that such technical deficiencies will plague also prospective studies which appear to be a more reliable approach to the all important exposure information, although the value of such studies in the past has suffered like that of retrospective investigations by an almost complete disregard of other environmental factors as important agents contributing to the causation of lung cancers (Lemon, Walden and Wood; Kaiho).

It is remarkable that despite the intense promotional activity expended in favor of the cigarette smoke theory of pulmonary carcinogenesis there are still competent and experienced investigators who doubt that this concept offers a satisfactory solution of the lung cancer problem (Hueper; Gagnon; Poche, Mittmann and Kneller; Higdon and Kirchoff; Marsden).

D.

Statistical Vagaries and Oddities

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There does not seem to be any agreement among the biostatisticians supporting the cigarette smoking theory whether pipe and cigar smoking is also a factor in favoring pulmonary carcinogenesis, although cigar and pipe smoke contain more 3,4-benzpyrene than cigarette smoke (Cardon, Alvord, Rand and Hitchcock). Stocks assigned to pipe smoking a limited increased lung cancer risk: "Male non-smokers are subject to a fifth or less of the general risk of lung cancer; pipe smokers to about half, and heavy smokers of cigarettes as a whole about twice the general risk." Lombard noted that pipe and cigar smokers showed only slightly higher rates than non-smokers.

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

Oberling also stated that cigar and pipe smoking do not carry the same lung cancer risk as cigarette smoking because the bitter and alkaline smoke of pipes and cigars is not inhaled. An editorial of the British Medical Journal commenting on a paper by Kreyberg mentioned that heavy cigarette smokers have a lung cancer rate per 100,000 of 363, pipe smokers of 41 and non-smokers in the Liverpool area of 131. Pernu observed from her appraisal of tobacco smoking upon lung cancer incidence in Finland that it was not possible to show that pipe smking had any effect on cancer of the respiratory system. Distinctly less optimistic was the assessment of Muddy who pointed out that, according to British and American statistics, pipe smokers as a class have approximately a 5-fold probability on the average of dying of lung cancer as non-smokers. Also Lombard conceded in a second paper dealing with this subject that cigar and pipe smokers had a 2.62 times the risk of lung cancer as did non-smokers. Biersteker and van Driel remarked that 1 out of 5 patients with lung cancer smoked pipes or cigars and that this seemed to cast some doubt on the presumed innocence of the habit. The most outspoken dissenter from this concept were Gsell; Gsell and Strobel; Abelin and Gsell; and Abelin. They found that in their Swiss patients with lung cancer only 40 per cent smoked cigarettes while the majority smoked cigars or pipes. For heavy cigar and pipe smokers the risk was 1.7 times that of cigarette smokers and 14.7 times that of non-smokers. They noted that their observations differed from those obtained in the United States but were compatible with findings in countries with a larger proportion of cigar and pipe smokers. These discrepancies were attributed to them to defective reporting in U.S.A. It is very doubtful whether this rather smooth explanation can account for such differences. The distinct suspicion must be entertained that more fundamental methodologic factors may account for them, as evident from a critical discussion of the role which inhalation of tobacco smoke allegedly assumes in determining the relative carcinogenicity of cigarette smoking, and the observation of Lombard that cigarette smokers who also smoked pipe and/or cigars had a lower lung cancer risk than those smoking cigaret-

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Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

tes at the same level of cigarette smoking.

C. Inhalation of Tobacco Smoke

When Doll and Hill found no differences between patients with lung cancer who inhaled and thosethat did not inhale, Cornfield et al.; Hueper; and MacDonald emphasized that this observation was contradictory to the existence of a smoking-lung cancer relationship. Doll and Hill's finding in fact is in fundamental disagreement with the basic exposure facts available for the action of occupational pulmonary carcinogens (Hueper, 1966). Rigdon and Kirchoff considered the observation of Doll and Hill as basic because pipe and cigar smokers usually do not inhale, although they have been included in several epidemiologic studies on the cigarette smoke role in the causation of lung cancer (Doll; Sadowski, Gilham and Cornfield; Watson and Conte; Wynder and Graham; Wynder and Cornfield). In these calculations the number of pipefuls of tobacco and/or cigars were converted into an equivalent number of cigarettes. According to Sadowsky's method of conversion three cigars were considered the equivalent of 30 cigarettes. Fisher argued in view of these negative findings that tobacco smoke had a negative relationship to lung cancer and cannot be directly carcinogenic Thus the validity of the cigarette theory was placed in jeopardy.

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It was fortunate, according to Doll, that his observations of the significance of inhaling cigarette smoke was not confirmed by subsequent investigators (Schwartz and Denoix; Lickint; and Breslow et al.). Hammond emphasized the fact that the degree to which cigarette smoke is inhaled determines the deverity of carcinogenic exposure. He ventured the opinion that most cigarette smokers inhale the smoke to at least a moderate degree, and that heavy smokers usually inhale the smoke deeply, while in contrast, pipe and cigar smokers usually avoid inhaling the smoke. He cited in support of this statement the data reported by the Tobacco Manufacturers' Standing Committee of Great Britain (Todd), that the proportion of cigarette smokers

who inhaled increases with the amount smoked, decreases with age, and is greater in men than in women. Hammond could confirm these British observations in a study done in the United States. About 84 % of all male cigarette smokers in Great Britain inhale and about 82 % do this in the United States.
A much more exacting analysis of the influence of inhaling cigarette smoke on the liability to develop lung cancer was reported by Burdette, who stated that, according to Hammond's findings, those who are currently smokers and do not inhale and belong to the age group 80-89 have a death rate of 11,857 per 100,000, those inhaling slightly 14,085, those inhaling moderately, 16,604, and those inhaling deeply, 21,545, while nonsmokers have a rate of 11,857. Schmähl, Consbruch and Druckrey as well as Galuskinova observed that 98 per cent of the 3,4-benzpyrene inhaled with cigarette smoke is removed in the lungs and no longer demonstrable in the exhaled smoke (Sula).

While the various observations incriminating inhalation as an important, if not essential, part in the process of bronchial carcinogenization appears to be reasonable, provided that sufficient justification of the cigarette theory can be evolved, the cited arguments still leave the problem of the action mechanism of cigar and pipe smoke almost entirely unresolved, and thereby creates some distinct uncertainty as to the acceptability of the concept related to the inhalation of cigarette smoke.

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Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

D. Direct Contact Action of Cigarette Smoke Condensate on Skin and Lips

During decades gone by when the smoking of clay pipes was in vogue, cancer of the lips at the site where "tobacco tar" was oozing through the p pipe stem and came in contact with the mucosa of the lips was an accepted cancerous response to tobacco tar (Bauer). Observations of more recent times do not indicate that the tarry substance oozing from the cigarette butt exerts an identical effect, although such contacts are intense, direct, and prolonged. In explanation of this curious phenomenon it is usually suggested that cigarette tar has a tissue specific action on the respiratory mucosa. The same proposal is advanced for disposing of the fact that the skin of the fingers of cigarette smokers are usually intensely brown stained for the same reason but have never responded with the development of a carcinoma at these sites. This lack of reaction is surprising, since the cigarette tar contains carcinogenic hydrocarbons which are in part identical with those found in coal tar which readily elicits cancers of the skin including that of the fingers in tar workers (Hueper, 1942). It may be possible that the rather low carcinogenic potency of cigarette tar when compared with that of coal tar is responsible for these observations.

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Cancers of the lower lip are not any longer attributed to tobacco tar but are ascribed to the action of solar radiation (Hueper, 1942; 1957; Ancev and Popov). On the other hand, there exists some evidence indicating that the combined action of tobacco smoke and burns in the oral mucosa associated with inverted smoking of cigars has been the cause of oral carcinoma among East Indians as well as among Panamanian Indians where this custom is common for economic reasons (Hueper, 1942; as well as inhabitants of the caribean area Haneveld; Quigley; Kini; Shirokov).

The alleged tissue specificity of cigarette smoke is thus a subterfuge for accounting for an observation not in accord with the cigarette theory.

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

E. Cancer of the Larynx, Another Part of the Smoke Tract

Since the larynx is a part of the respiratory conduit through which the inhaled air as well as the tobacco smoke must pass so as to get into the lung, it appears natural that supporters of the cigarette theory have associated the causation of cancer of the larynx with the smoking habit (Wynder; Jackson and Jackson; Roffo; Heermann; Schrek). The epidemiologic data on the frequency of larynx cancer in Great Britain, however, do not support such an association. Kennaway stated in 1953 that in contrast to the rising rate of lung cancers that of larynx cancers had remained static (Blalock, Kennaway, Lewis, Urqyhart). There was a distinct discrepancy in the larynx cancer rates in males in England and Wales from that seen in females as the number of persons producing one death from larynx cancer in metroplitan and rural areas. While the pattern for males followed that seen with lung cancers, that for females followed an opposite trend. Larynx cancers in males were also more frequent among members of the lowest eonomic class than among members of the upper ones (Kennaway and Kennaway).

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Larynx cancer morbidity studies conducted in the United States, on the other hand, have shown an increase between 1937 and 1947, which was abt quite twofold between 1914 and 1930 (Milmore). It is significant that no information is available from the United States about any causal role of occupational factors in their causation, while a moderate amount of data on this aspect have been reported from European countries (England, Germany, Italy, Czechoslovakia (Stocks; Kennaway and Kennaway; Bluemlein; Cadotsch; Blaha; Kolomaznik, Zdrazil and Picha; Fior) (restaurant workers, Metallurgical workers, metal grinders, cardroom jobbers, tobacco manufacturers, gas workers, lithographers, engravers, blast furnace men, foundry workers, welders, electroplaters, blacksmiths, engine drivers, asphalt heaters stokers). The present failure to assess environmental and occupational causal factors in the induction of larynx cancers thus creates the same statistical bias that prevails in regard to the role of tobacco smoking in the genesis of lung cancer.

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

F. Cessation of Smoking

The statistical studies of several supporters of the cigarette theory have yielded another rather surprising and unique biologic observation which scarcely harmonizes with our previous knowledge about the effects of carcinogens on tissues of man and animals, about the persistence of such effects and about the appearance of cancers many years after the cessation of exposure to various occupational carcinogens (Hueper, 1966; 1942; Hueper and Conway, 1965). In two extensive epidemiologic analyses of the fate of individuals who stopped ciggrette smoking Hammond and Horn interpreted their statistical data to mean, that the carcinogenic effect of cigarette smoking upon the lungs was reversible and that this phenomenon was responsible for the progressive decrease in the degree of former smokers to develop lung cancers with the passing of time after cessation of smoking. According to Hammond and Horn, a reduction in the lung cancer risk in former cigarette smokers was demonstrable already after one year following cessation of the habit. The decrease progressed during the first 10 years after this event so that after more then ten years the mortality rate from lung cancer of former cigarette smokers approached that of nonsmokers (Hammond and Horn, 1954, 1959). Similar observations were reported subsequently by Doll as the result of a statistical analysis of the fate of British physicians who were surveyed in a prospective study for the effects of this habit on their liability to develop lung cancers. The highest mortality rate was found among physicians who stopped smoking at the time the questionnaire to them was issued (1.03 per 1,000), those who had ceased smoking during the 10 years preceding this procedure had a lung cancer death rate of 0.59 per 1,000, while this stood at 0.36 per 1,000 for those who had stopped smoking more than 10 years before the survey was started. Cornfield et al. commenting on these observations claimed that the statistical data indicated also that the magnitude of the reduction of risk following discontinuation

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Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

of smoking depended on the amount of cigarettes previously smoked. Ochsner also endorsed the concept of the non-permanence of the carcinogenic damage from cigarette smoking on the bronchial mucosa. He asserted that the incidence of lung cancer among cigarette smokers who had stopped this habit for more than 10 years dropped to 8.3 per 100,000 ,approximating that observed for nonsmokers(3.4 per 100,000),while the rate was 57.6 for smokers who continued to smoke the same amount as formerly consumed by the discontinued smokers. These statistical results received support from the histological observations recorded by Auerbach et al. on the type and frequency of"precancerous" lesions found in the bronchial mucosa of smokers and discontinued smokers. Auerbach maintained that the condition of the bronchial mucosa of former smokers approached progressively a normal state with the passage of time after cessation of smoking. In a recent investigation of Moore concerning the relative tendency of the development of second primary cancers in the larynx of cigarette smokers following the eradication of the first cancer, it was noted that continued smoking accentuated the frequency of second primary cancers(21 cases among 65 within 5.7 years of observation),while cessation of smoking was followed by a reduction of such events(2 cases among 37). Delarue accepting these observations as factual and valid, proposed that even heavy smokers of long duration would benefit from a cessation of smoking.

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In commenting on the significance of the claims cited recently Kotin remarked that if cigarettessmoke represented the source of the dose,it would perform its ultimate effect independently of the removal of the carcinogen. This statement is doubtlessly correct as far as carcinogenic effectivess is concerned seen in experimental animals given optimal or supraoptimal doses of chemical carcinogens(Hueper and Conway,1965). However, after the administration of a carcinogen in a single maximally effective dose, the delayed cancerous effects often do not become apparent in all animals

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

but only in a varying portion depending upon the carcinogen, the route of administration and the vehicle used in which the carcinogen was contained. When, on the other hand, carcinogens are administered in minimal effective doses by repeated introduction given in longer intervals the carcinogenic effectiveness of the same dose as that given by single administration is not only much more intense but also lasts longer after the treatments have been stopped (Payne and Hueper). It is this type of carcinogenic exposure which prevails for man smoking cigarettes and inhaling carcinogens containing cigarette smoke. Experiences in experimental carcinogenesis thus make it most unlikely that a reduction of the lung cancer risk from cigarette smoking should become manifest and demonstrable as early as one year after such an event as claimed by Hammond and Horn.

This conclusion receives ample support from observations made with the appearance of occupational cancers affecting the lung, skin, and bladder many years after the cessation of exposure to the causal agent (radioactive chemical, asbestos, chromates, coal tar, aromatic amines, etc.) (Hueper, 1942; Hueper and Conway, 1965; Hueper, 1966). Students of these cancers have always emphasized the fact that cancers will continue to appear for some 15 to 20 years following the elimination of an occupational carcinogen from the industrial environment, among the workers once effectively exposed. 2015031759

Experimental and occupational cancerologists are moreover familiar with the fact that the primary abnormal anatomic changes elicited in tissues after contact with a carcinogen may completely recede after arrest of exposure. However, the apparently normal tissue which then evolves retains its carcinogenic sensitization to a high degree, since a cancerous reaction may speedily follow upon a re-exposure with the carcinogen, indicating that the once exposed tissue has not returned to an actually normal state. The observations of Auerbach on the bronchial mucosa of former smokers may and probably are deceptive as to their significance in potential carcinogenic respects.

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

The experiences available on this aspect from human and animal observations strongly indicate that their remains a distinct degree of residual cancerisation in tissues once exposed to chemical carcinogens even in the presence of apparently normal cellular structures.

There exists indeed some statistical evidence which may possibly be interpreted in this sense. Several statistical studies of physicians, who form a socioeconomically rather uniform group, concerning their cigarette smoking habits (Wynder and Cornfield; Snegireff and Lombard; Doll and Hill) have shown that members of this population group are not only cigarette smokers but have been impressed by the evidence advanced in regard to the lung cancer risks connected with this habit that they have abandoned in many instances this habit. Doll and Hill reported in 1964 as the result of this development a decline of lung cancer mortality among British physicians in the face of a 22% increase among the general population of this country. Since the Surgeon General of the U.S.Public Health Service has publicly announced that about 100,000 American physicians have lately given up the smoking of cigarettes, by extrapolating data obtained in a survey of 5,356 pysicians(Garfinkel). it is depressing to note that ,according to records published in the Journal of the American Medical Association in 1965, there has not been an decrease but an increase in deaths from lung cancer among members of the medical profession in the United States(Rogers). While the 1958 [illegible] cancer deaths among American physicians were due to lung cancer, the percentage stood in 1964 at 14.5 %; it was in 1955 for male physicians under age 70 at 11.5 % and was in 1965 at 18.1 %. Before drawing any definite conclusions from the allegation of the Surgeon General, it might be wise to take another critical look at the death statistics of physicians which might give a real clue concerning the actual effectiveness of such events in the face of competently checked figures on the changes of smoking habits among members of the medical profession.

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Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

G. Alcohol and Coffee, Some Surprising Statistical Associations

Stocks reported in connection with his studies of lung cancer and its causes in the Liverpool region that the consumption of beer had a positive correlation to lung cancer, and that this association was demonstrable in males regardless whether they were non-smokers, cigarette smokers or pipe smokers, and that therefore this phenomenon could not be explained by the assumption that drinking and smoking often go together, as asserted by Pernu who made a similar statistical observation among male drinkers in Finland. It is remarkable that no association was found in France between the consumption of wine and lung cancer, that, on the other hand, coffee drinking appeared to be associated with a tendency to lung cancer development, which again was independent from smoking habits. Since it is not likely that beer or coffee are inhaled, one is left wondering what the causative agent and causative mechanism are which are responsible for these surprising statistical correlations, and what the existence of such correlations actually signify as to the causation of lung cancers. Pernu wisely decided that heavy drinkers are also smokers, and alcohol could also be inhaled thereby proving an explanation for the statistical correlation between alcohol and cigarette habits to lung cancer.

H. Histological Types of Lung Cancers and the Types and Frequency of Metaplastic Bronchial Lesions

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One of the various kinds of evidence most frequently cited in support of the cigarette theory relates to the relative frequency of the different types of lung cancers and their purported positive association with cigerette smoking. In 1954 Kreyberg divided lung cancers into two groups which he thought were etiologically distinct. Carcinomas of group I composed of squamous cell, large cell and small cell carcinomas were, according to Kreyberg, induced by external factors, such as especially cigarette smoking and atmospheric pollutants. Adenocarcinomas and bronchial adenomas forming group II and found equally frequent in males and females were attributed by Kreyberg to endoge-

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

nous or constitutional factors. This concept received in 1957 a distinct direction in support of a cigarette smoke origin of all cancers represented in group I, when Doll and Hill demonstrated a close statistical relationship between the amount of tobacco smoked and the development of type I carcinomas. Adenocarcinomas did not exhibit any relationship to smoking, on the other hand. Kreyberg then advanced the thesis that any change in the ratio of cancers of group I to those of group II was indicative of the occurrence of a change in the quantity and quality of the environmental respiratory carcinogenic spectrum, i.e. for all practical reasons in the frequency of cigarette smoking and of the number of cigarettes smoked, as subsequently interpreted, because of the observed proportional increase of group I carcinomas during more recent years simultaneous with the increased consumption of cigarettes (Wynder), their preponderance in males and male cigarette smokers (Ravenholt and Foege; Auerbach; Hillis and Cameron). Rakover and Kallner while able to confirm the linkage between histology and the smoking patterns with a preponderance of adenocarcinoma among nonsmokers, of the sex distribution, i.e. the more frequent occurrence of adenocarcinoma in females over males, and the age distribution, i.e. the higher frequency of adenocarcinomas during younger age groups, they failed to demonstrate that there was a parallelism between lung cancer frequency and degree of cigarette smoking for the two ethnic groups composing the population of Israel. While members of both groups (occidental and oriental) showed a proportion of 3 to 4:1 of group I to group II carcinomas, there was a much higher lung cancer rate among the cigarette smoking occidental population group. They concluded that there is a discrepancy between the theory that pulmonary cancer should be caused or, at least, severely influenced by cigarette smoking and the prevalence of this cancer in a population group for which no higher degree of cigarette smoking could be established than the one found in a low-incidence group.

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Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

Whereas Kreyberg adhered in his monograph on histological lung cancer types(1962) still to his original concept and cited in support of it the striking similarity between the British and Norwegian materials as to proportion of histological types and magnitude of cigarette risk, he had to concede in an analysis of lung cancers in Venice(Ferrari and Kreyberg), where according to the opinion of these authors cigarette smoking played the principal reason for a marked increase in the number of lung cancers, an unexpectedly high number of adenocarcinomas(group II cancers) were found(Witwell). Although Ferrari and Kreyberg were inclined to assume that this exceptional behaviour of Venice cancers might be attributable to the relatively small number of cancers analyzed, the experience did not remain unique for long. Herman and Crittenden examining the distribution of lung carcinomas as to histological types as observed at autopsy at the Los Angeles County Hospital noted that the proportion of epidermoid carcinomas(group I) in men was not increased, while the proportion of adenocarcinomas apparently was rising. Snelling and Mun Kam reported an unusually high incidence of nonsmokers with squamous cell carcinoma and added that lung cancer incidence is high in Chinese who smoke, but it is low among Malayans who also are heavy smokers. Ashley and Davies remarked that cigarette smoking was associated with adenocarcinoma just as strongly as with the group of squamous and undifferentiated tumors. An unusually high percentage of adenocarcinomas (27.5 in males and 30.0 in females) was reported by Takeda from Japan, while there were only 28 % squamous cell carcinomas in males and 8.3% in females, while undifferentiated cell cancers amounted to 45 % and 56.0 %, respectively. Lee and Tso analyzing 228 cases of lung cancer in Hong Kong seen in Chinese revealed that adenocarcinomas were the most frequent type, followed by undifferentiated cell carcinoma, squamous cell carcinoma and oat cell carcinoma.

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Source: https://www.industrydocuments.ucsf.edu/docs/mzyk0000

These observations contrast sharply with those made by Spain in New York, where the autopsy incidence of adenocarcinoma has remained relatively constant over a 45 year period (1912-1956), while there has been a rise in the proportion of squamous cell and undifferentiated cell carcinoma among the increased number of lung cancers which came to autopsy.

According to the compilations of Hueper on 381 occupational cancers of the lung on which a histological diagnosis was available and which were caused by contact with arsenic, chromium, nickel, asbestos, silica, ionizing radiation, coal tar, mustard gas, 41 % were squamous cell carcinomas, 49 % were undifferentiated cell carcinomas and 10 % were adenocarcinomas. Dorn reported from his nation-wide study of lung cancers that 29.3 % were squamous cell carcinomas, 61.2 % were undifferentiated cell carcinomas and 9.5 % were adenocarcinomas. Since adenocarcinomas were obtained in addition to the other two types of cancers of the lung in animals after an experimental administration of these carcinogens, it is most improbable that the various histological types of lung cancers have any relation to the etiologic factors and therefore give any information as to the relative share which cigarette smoking may contribute to the total cancer incidence.

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An identical judgement is indicated concerning the allegation of Auerbach et al. that the frequency and type of metaplastic changes seen in the bronchial mucosa reflect a cigarette smoke genesis in smokers. Squamous cell metaplasias have been seen in infants at the age of two years (Gere, Abel and Shields) even in the absence of prominent disease, and are not regarded to be precancerous in nature. They have been observed by various investigators in a number of diverse pulmonary as well as other diseases (pneumonia, chronic inflammatory diseases of the bronchi, influenza; bronchopneumonia, diphtheria, syphilis, lung cysts, whooping cough, tuberculosis, uremia, myocardial infarction, occupational exposure to chromates, asbestos, silicosis with radioactive dust, and arsenicosis (Berkheiser; Sanderud; Hacken-

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

TABLE 11.—*Sex Distribution of Lung Cancer in the United States and Selected Foreign Countries, 1850-1953*

Country	Year	Author	Male-Female Ratio
United States	1933	Dorn	5:1
	1951	Moore	6.6:1
	1947	Humphreys	7:1
	1950	Beeler et al.	11.5:1
	1946	Lindskog	4.5:1
	1951	Carlisle et al.	29:1
	1941	Halpert	14:1
	1951	McBurney et al.	29:1
	1949	O'Keefe	20:1
	1941	Farberow and Baslow	13.5:1
	1935	Neely	1:1
Mexicans*	1953	Steiner	1:0.7
Norway	1953	Kreyberg	4:1
	1925	Kreyberg	1:1
Sweden	1947	Henschen	2:1
Denmark	1931	Clemmesen	4:4
	1945	Clemmesen	3:1
Austria	1953	Denk	15:1
Germany	1953	Grosze	6.6:1
	1850–1899	Grosze	1.8:1
	1900–1919	Grosze	3.1:1
	1920–1929	Grosze	3.8:1
	1930–1939	Grosze	3.8:1
	1940–1949	Grosze	5.4:1
France	1952	Lemoine	10:1
Canada	1948	Gagnon	8:1
Argentina	1947	Santas	50:1
England	1949	Mason	10:1
	1949	Fulton	7.3:1

* Mexicans living in Los Angeles.

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Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

sellner; Witkowski; Delarue and Chomette; Ford, Fidler, and Lock; and Tarantini, Chiurco). While this evidence does not refute the possibility that cigarette smoke can elicit also metaplastic bronchial changes, the large number of conditions which have a similar effect militate against the claim that cigarette smoking is the principal cause of such manifestations and that a lowered frequency in former smokers and nonsmokers supports such allegation and represents a morphological manifestation that such "precancerous" lesions are reversible and their presumed disappearance in exsmokers provides proof of the reversibility of a lung cancer predisposition created by former cigarette smoking (Auerbach et al.). Indeed, Cunningham and Winstanley noted that the bronchial epithelium of heavy smokers might be perfectly normal morphologically.

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I. Aspects of Sex

Cancers of the lung have in common with cancers of several other sites, such as skin, bladder, oral cavity, and esophagus, the peculiarity that they are in general much more common in males than in females. (Table 46) While it has been suggested that these discrepancies in sex distribution are somehow related to sex-hormonal conditions (Kotin), statistical appraisals of Haenszel Korteweg also emphasized the "non-hormonal character of the female age curve and Shimkin have not yielded any support to this assumption as far as lung cancers are concerned. In fact, experiences with the other cancers revealing sex differences in frequency indicate that the real underlying reasons for such phenomena are associated with differences in the exposure to carcinogenic agents which members of the two sexes sustain. For instance, cancers of the bladder are more common among Bantu women than men in Mozambique because they do the agricultural labor and for this reason sustain more often infections with Schistosoma hematobium which affect the bladder and induce cancers of this organ. Cancers of the oral cavity are found more often in Filipino women

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

than in Filipino men, because the women indulge more often in chewing betelnut quids, which is a habit underlying the development of oral cancer in these areas. Observations on the sex distribution of asbestos cancers of the lung indicate that with an equalization of occupational exposure to asbestos there occurs an equalization of lung cancer risks for members of the two sexes (Hueper, 1966).

A striking characteristic of the marked differences in the frequency of lung cancer for the two sexes recorded from most countries is the existence of considerable variations in the degree of this discrepancy for different countries and demographic groups. (Segi; Davies, Walker and Best; Hueper, 1955; Dungal; Kallner; Steiner) These differences in the male:female lung cancer ratio may vary from 1.5 :1 to 11:1 or more. Such observations militate against the operation of a sex-conditioned, constitutional factor and favor the determining influence of an exogenous factor or environmental factors. Since tobacco smoking has been traditionally a male habit and has been adopted to some but growing extent only during rather recent times by members of the female sex, supporters of the cigarette theory have argued that the differences in lung cancer rates between males and females are mainly attributable to such habitual fluctuations and that the recent rise in frequency of lung cancer among women relates to their increasing indulgence in cigarette smoking. They support this reasoning by pointing to the fact that the great majority of women having squamous cell carcinomas were smokers, while those with adenocarcinomas the prevalent histologic type among females were nonsmokers (Doll; Wynder; Hammond; Haenszel, Shimkin and Mantel).

2015031767

While this explanation may be satisfactory to those who have become convinced that cigarette smoking accounts for the recent development in the epidemiology of lung cancers, it has not been accepted by others and apparently more critical investigators who have pointed to some serious inconsistencies and deficiencies in the evidence supporting the cigarette causation of these sex related differences. Raker as well as, Kahler commenting on the surprisingly high lung cancer rates among occidental female Israelites noted that there was no evidence indicating that Israeli women were especially heavy cigarette smokers.

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

The same argument may be applied in regard to the high lung cancer rate of women in Iceland (Dungal; Thorarinsson et al.) and of Mexico-born women in California (Steiner; Buechley et al.). According to Myddleton, there is a peculiarly high female lung cancer rate among women residing on the Channel island, Jersey, since it is almost twice as high as that recorded for women in Great Britain. Phillips and Owchar studying the cancer mortality trends in Canada between 1941 and 1958 comment on the fact that there was a significant increase in male mortality from cancers of the respiratory system, while no significant change occurred in the female mortality (Phillips, 1961). Also Best remarked on the lack of any dramatic alterations in the female lung cancer rates in Canada between 1931 and 1960. In the United States, by contrast, the death rate per 100,000 women stood at 4.6 during 1950-52 and had risen to 5.6 during 1958-60, and had reached 6.9 in 1963. It is not readily apparent that such a different behaviour in female lung cancer trends in two neighboring countries with similar ethnic populations and economic conditions are fundamentally reflections of marked differences in the smoking habits of the women.

Recent observations by Haenszel on the lung cancer rates among female immigrants into the United States seem to support this doubt. He found that when foreign-born immigrant females were compared to males from six countries (Mexico, Norway, Russia, Sweden, Italy, Ireland), the females had a higher lung cancer rate than the males. In addition the female immigrants of 11 countries showed an excess lung cancer rate, some of very marked degree, over the native U.S. females. Haenszel commenting on these observations stated that these variations in the male-female lung cancer ratios among the immigrants and the differences in rates among the female immigrants and the United States natives cannot be explained on the basis of cigarette smoking.

2015031768

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Hueper(1955) who also questioned the exclusive roleassigned to cigarette smoking by supporters of the cigarette theory as cause of the distinct fluctuations in the sex ratio of lung cancers proposed that they are more likely attributable to differences and alterations in the type and extent of the action of a broad spectrum of environmental respiratory carcinogens affecting the members of the two sexes to different degrees. He pointed out at that time that males are more extensively employed than women in occupations which produce and use known or suspected atmospheric carcinogens(Hueper,1966) and that males are more consistently than women employed over longer periods of their lives in such occupations. Males predominate also in outdoor occupations,especially in urban areas,where they become exposed to carcinogenic atmospheric pollutants(effluents of domestic and industrial furnaces,exhaust from gasoline and diesel engines,dust from rubber tires and from asphalted and oiled roads). Males are more often than females performing heavy physical labor requiring deep and frequent respiratory movements which facilitate the penetration of larger amounts of carcinogenic air pollutants into the distal portions of the respiratory tract and thich increase thereby the frequency and degree of exposure. Males more often than females work through the entire life span of their occupational life within polluted urban areas,while women stay for larger period of their lives in the cleaner suburban dormitory communities and within the confines of their homes.

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As the chemical analyses of Dikun have shown that women living mainly as house wives also sustain exposures to carcinogenic hydrocarbons generated from heating devices,cooking stoves(wood,coal,gas),kerosene lamps,smoking of meats and fish under home conditions,and frying and broiling of foodstuffs especially meats and fish (Dikun;Dikun et al.;Grimmer and Hildebrandt;Stcoks;Hueper; Lijinsky and Shubik;Sula;and others). The increasing employment of women in industry and commerce and their use of automobiles have become another

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

major environmental source of contact with carcinogenic agents acting on the respiratory organs(Boucot and Percy). If Blümlein and Schmidt claimed that the cigarette theory is the only hypothesis which provides a reasonable explanation for the sex differences in the frequency of lung and larynx cancers, they apparently have not given this matter sufficient thought and attention. The increasing lung cancer rate among women may well be associated with the various nontobacco factors listed and may have little or no connection with cigarette smoking.

Mention may finally be made of another source of contact with environmental agents which have received so far very little consideration,i.e. the exposure to carcinogenic medicinal agents. While reports on an arsenical causation from the use of pesticides in vineyards have rather conclusively proven the existence of a serious lung cancer hazard from such contacts,very litlle data extend such risks to the widespread use of arsenical medicinal preparations(Hueper,1967). The possibility or probability of arsenical medicinal cancers of the lung in women was recently raised in a paper by Dörken. He reported that among 290 women with lung cancer 20 had received arsenical medication for the control of syphilis(6.9 per cent). Histologically two of these cancers were adenocarcinomas and 18 were squamous cell or undifferentiated cell carcinomas,while 2 were pleural mesotheliomas. This latter type of cancer has aroused during recent years special interest because of its rapidly growing frequency in individuals who had occupational or general environmental contact with asbestos,a well established pulmonary carcinogen.

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It seems to be pertinent to scrutinize also the rapidly spreading use of sprays in and around the house(pesticides,hair lacquers, waxes,polishes,stove cleaners,cleaners,etc.) for carcinogenic effects upon the respiratory system of their users,since they doubtlessly entail through proper and even more so by improper use massive inhalation of the active principles as well as of their vehicles by their users in home and garden.

Source: https://www.industrydocuments.ucsf.edu/docs/nzyk0000

It is obvious from the evidence presented that the allegation concerning a predominant role of cigarette smoking in the causation of lung cancer among women and of the rising frequency of this cancer in women deserves serious reappraisal because of the existence of aigreat deal of important and valid epidemiologic evidence contradicting such a claim.

K. Age Aspects

Various age aspects of lung cancers have been used for ascertaining their significance to etiologic factors,especially cigarette smoking. It has been known for some time that the manifestations age of occupational cancers ,such as those of the bladder caused by aromatic amines,cancer of the scrotum induced by contact with coal soot, medicinal arsenical cancers of the skin, has exhibited a direct relation to the age at onset of exposure to the carcinogens involved(Hueper,1952). A shift into younger age groups was observed also for cancers of the lung induced by the inhalation of tar fumes,and possibly radioactive gases and dust,when the age distribution of these cancers was compared with that found in the general population.

2015031771

When Passey studied the relation of the age distribution of lung cancers among smokers of different severity he found to his surprise that the average manifestation age of lung cancers did not vary significantly between heavy smokers from that of mild smokers,nor did the youngest to commence smoking had a different average manifestation age from that of the late starters. This experience resembled thus that noted for the conditions prevailing for occupational cancers of the lung in nickel and chromate workers,

Source: https://www.industrydocuments.uesf.edu/docs/nzyk0000

who showed an age distribution of cancers of the lung independent from their entry into the industry. Pike and Doll confirmed the correctness of Passey's claim that neither amount smoked nor age at start of smoking were affecting the age at which the lung cancers became manifest in cigarette smokers. Doll and Pike, however, took exception to the conclusion of Passey that his observations indicated that cigarette smoke did not act as a carcinogen, because the average age at onset of lungecancer in hospital patients appeared to be almost the same irrespective of their daily consumption of cigarettes. In refutation of Passey's contentions they asserted that cigarette smoke is not a strong carcinogen but a weak one which was unable therefore to influence the manifestation age in dependence upon the age at onset of smoking and upon the amounts of cigarettes smoked. Buechley in an investigation of this problem in California pointed out that there were no age differences in the appearance of cancer in males and females, although females tended to smoke less than males. He noted, however, that in his material the age at onset of lung cancer revealed an inverse relation to the amount of cigarettes smoked which was higher in young persons than in old ones. The manifestation age of the resulting cancer, on the other hand, remained the same. It would appear from these observations of Buechley that the process of cancerization starts after onset of exposure, i.e. earlier in the young than in the old starters, but the preparatory period is longer in the young than in the old thereby insuring about the same manifestation age. Wicken has also dealt with this problem of relation between average age at death from lung cancer and different amounts of cigarettes smoked, by subjects in Northern Ireland. The average age at death by males nonsmokers was 63 and by female nonsmokers was 67. Individuals smoking 1-10 cigarettes daily died at age 61 for males and 63 for females; Individuals smoking 11-22 cigarettes per day had an average age at death of 61 for males and 57 for females; while heavy smokers consuming daily more than 23 cigarettes died at age 60 regardless of sex.

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While the cited data suggest that differences in amount of cigarettes smoked do not seem to influence the average manifestation age of lung cancers observed in smokers, there can be no doubt that the process of canceri-zation begins in the human bronchial mucosa exposed to a carcinogen the moment the first contact is established (Brooke; Hueper and Conway, 1966). It may be argued therefore than the recent tendency for boys and girls to start smoking at an earlier age than heretofore (Salber, Goldman, Buka and Welsh) might favor the appearance of lung cancers at an earlier age, despite the reported failure to demonstrate any relation between the relative amounts of cigarettes smoked and the manifestation age of lung cancer. Such observations have recently been reported by Schinz and Reich who found a shift into younger age groups for lung cancer in England and Wales when comparing the age distribution for 1952-54 with that in 1926-30. Similar findings were reported by Hood, Campbell, Dooley and Dooling from observations made among lung cancer patients in a U.S. Air Force Hospital, where since 1958 a total of 33 persons between the ages of 21-39 years and an average age of 34 years were found among 144 cases with lung cancer. Cohort analyses of Swedish recently born cohorts are, according to Klebba, at higher risk of dying from lung cancer at younger ages then their predecessors in the United States. The analyses of Lombard and Snegireff also showed that the earlier smoking is begun, the higher is the eventual prevalence of lung cancer.

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While all these observations have been used as evidence bolstering the merits of the cigarette theory since they reflect coincidental statistical relations with possible causal implications, there are a few pieces of evidence which point to other environmental factors. Mills noted that astonishingly high old-age lung cancer rates exist in Cincinnati coming on a full decade earlier in the most polluted sections of the city than in the clean ones. It is significant that Phillips reported that the mortality rate of lung cancer lagged some 10 years behind the rate in England, which

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